

Applicant : Morris, et al.  
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Attorney's Docket No.: PP023697.0001/ 20366-005001

## **REMARKS**

Claims 20-31 were pending in the application.

Claim 22, withdrawn from consideration as directed to a non-elected invention, and claims 20-23, 28, 30 and 31 were cancelled without prejudice to presentation in related applications.

Claims 24-27 and 29 were amended to further clarify the claimed invention. New claims 32-36 were added. Support for the amendments to claims 24-27 and 29 and for new claims 32-36 can be found throughout the application as originally filed.

No new matter has been added.

Upon entry of this amendment, claims 24-27, 29 and 32-36 will be pending.

## **Claim Objections**

Claims 20, 21 and 23-31 were objected to for encompassing unelected inventions. Claims 20, 21, 23, 28 and 30-31 have been cancelled without prejudice. Applicants have amended the remaining pending claims to remove reference to unelected inventions. Accordingly, Applicants request withdrawal of the objections to the claims.

## **Rejections under 35 U.S.C. §112, second paragraph**

Claims 20, 21 and 24-31 were rejected as allegedly indefinite. Although Applicants respectfully assert that one of skill in the art would readily understand the metes and bounds of the claims, Applicants have amended the claim set to further improve the clarity of the claims.

Claims 20, 21, 28 and 30-31 have been cancelled without prejudice.

Claims 24-31 were said to be indefinite due to the recitation of the phrase "unaffected individual" in claims 24 and 27. Claims 28 and 30-31 have been cancelled without prejudice. As amended, claims 24 and 27 no longer recite the phrase "unaffected individual".

Claims 24-26 were said to be indefinite as the Office alleged that it:

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is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 50% decrease.

Claims 24-26 have been amended. As amended, the claims specify that there is a 50% decrease in the patient sample as compared to the second sample. Also, the claims no longer recite a “predisposition to cancer.”

Claims 27-31 were said to be indefinite as the Office alleged that it:

is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 50% decrease.

Claims 28 and 30-31 have been cancelled without prejudice. Claim 27 has been amended. As amended, claim 27 specifies that there is a 50% decrease in the patient sample as compared to the second sample. Also, claim 27 no longer recites a “predisposition to cancer.”

Claim 29 was said to be indefinite as the Office alleged that it:

is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 100% decrease.

Claim 29 has been amended. As amended, claim 29 specifies that there is a 100% decrease in the patient sample as compared to the second sample. Applicants note that claims 24 and 27, from which claim 29 depends, were amended to remove the phrase “predisposed to cancer.”

Claim 24 was said to lack sufficient antecedent basis for the recitation “the level of mRNA in (a)”. Claim 24 was amended to further clarify the claim language.

Claim 24 was also said to lack sufficient antecedent basis for the recitation “a level of the mRNA in a second sample”. Claim 24 was amended to further clarify the claim language.

Claim 24 was further said to lack sufficient antecedent basis for the recitation “a level of the mRNA in a third sample”. Claim 24 was amended to further clarify the claim language.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

**Rejections under 35 U.S.C. §112, first paragraph (enablement)**

Claims 20, 21, and 23-31 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to provide adequate enablement. Although acknowledging that the specification was enabling for “diagnosing prostate cancer comprising detecting an increase in Egr-1 gene expression (SEQ ID NO:167) in a normal prostate tissue”, the Office alleged that the specification failed to:

provide enablement for a method of diagnosing every other type of cancer [in addition to prostate cancer] comprising detecting just any change in expression of just any CA gene in just any type of sample, as compared to any type of sample. Further, the specification does not enable any kind of diagnostic assay wherein one would be able to predictably determine whether someone has a predisposition to any cancer by measuring expression of EGR-1 (SEQ ID NO:167) in any sample.

Applicants do not agree.

Preliminarily Applicants note that claims 20, 21, 23, 28 and 30-31 were cancelled without prejudice. Claims 23, 24-27 and 29 were amended. For example, claims 24-27, 29 recite that the methods are diagnostic for colon cancer while claims 32-36 recite that the methods are diagnostic for prostate cancer. The claims further specify that a decrease of at least 50% in the expression of a sequence comprising SEQ ID NO:167 in the patient sample as compared to the second sample is indicative of colon cancer (claims 24-27, 29) or prostate cancer (claims 32-36). Finally, the claims were also revised to recite that the second sample comprises either non-cancerous colon or non-cancerous prostate tissue.

The Office alleges that it would require undue experimentation to determine whether the expression level of SEQ ID NO:167 is indicative of *every* carcinoma or indicative of a predisposition for *every* cancer. As discussed above, the claims have been revised and no longer recite methods of *every* carcinoma, instead specifically identifying colon and prostate cancer.

Also, as amended, the claims do not recite methods for diagnosing whether patients have a predisposition to one or more types of cancer.

The standard for enablement is that the specification teach those of ordinary skill in the art how to make and use the invention without “undue experimentation;” *see MPEP § 2164.01*. The standard is not, as the Office asserts, “irrefutable” evidence, *e.g.*, of a linkage between a marker and a disease state. “Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *See In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Moreover, the test for undue experimentation is not “merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . . .” *See Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). Finally, “[t]he law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention.” *See Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338 (Fed. Cir. 2000).

Applicants respectfully submit that no undue experimentation would be required for a person of skill in the art to practice the presently claimed methods. This is particularly true given the level of skill in the art, the state of the art, and the teachings of Applicants’ specification. First, the level of skill in the art can be characterized as being quite high. Clearly, those of skill in the art would have been quite capable of measuring levels of sequences comprising SEQ ID NO:167 without undue experimentation. The specification and the state of the art as of the priority date of the present specification are replete with guidance as to how to isolate and detect EGR1 mRNA in both cell and tissue samples.

The Office summarizes that practicing the claimed methods would require undue experimentation to determine if “the method would function as broadly claimed.” The methods are not broadly drawn to *every* cancer, *any* change in expression level, or using *any* control. The claims, as amended, are directed to colon or prostate cancer. The claims recite a specified degree of reduction of expression as indicative of these specific cancers. The claims specify controls comprising non-cancerous colon or non-cancerous prostate tissues. The “exhaustive

“experimentation” referred to by the Office is simply not present. Any experimentation necessary to practice the claims as amended would clearly be routine.

Applicants respectfully redirect the Examiner to *In re Wands*, in which the court stated that “The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed” (citing *In re Jackson*, 217 USPQ at 807 ((Bd. App. 1982)). Thus, given the high level of skill in the art, the guidance provided by Applicant’s specification, and the reasonable amount of experimentation involved, no undue experimentation would have been required for a person of ordinary skill to carry out the presently claimed methods. As such, the claims are fully enabled.

Applicants further point out that the Eid reference cited by the Office (Cancer Research 58, 2461-2468) supports the enablement of the pending claims. As acknowledged by the Office, Eid “demonstrates that an increase in Egr-1 expression in prostate biopsies from a subject, as compared to Egr-1 expression in normal prostate tissue, is indicative that said subject has prostate cancer.” Accordingly, the Office is acknowledging that the present application teaches how to measure Egr-1 levels and correlate the levels to the presence of prostate cancer. The same methods would be used to correlate reduced levels of Egr-1 to prostate cancer and colon cancer. Applicants note that Eid discloses that in certain carcinomas (for example lung, breast carcinoma, glioblastoma and osteogenic sarcoma) absence of expression (i.e. a decrease from control) of Egr-1 is correlated with cancer. Further, Eid states that “Our studies demonstrated a significant increase in expression of EGR-1 in tumors with more aggressive morphology compared with less aggressive tumors.” Accordingly, the difference in expression as an indicator of prostate cancer seen in Eid as compared to the present application (Eid indicates increased expression is indicative of prostate cancer while a decrease in expression is claimed in the present invention) may be a function of the nature of the tumor cells tested (i.e. aggressive tumors vs. less aggressive tumors).

Further, it appears that the Office is requiring as proof of enablement information and data outside the scope of the enablement requirement. For example, the Office cites several

references discussing, *inter alia*, considerations necessary in bringing a cancer biomarker to successful **clinical** application. The Office alleged that if expression of a gene was to be used as a surrogate for a diseased state, some disease state had to be identified with the molecule; that research must validate the markers against acknowledged disease end points; that quantitative criteria for marker presence and absence had to be confirmed in prospective population trials; and that the sensitivity and specificity of a biomarker must be validated against a known cancer outcome, including testing the marker on clinical material obtained from subjects monitored in advance of clinical cancer and then irrefutably linking marker results with subsequent histological confirmation of disease. Indeed, the Office stated “this irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker” (emphasis added). In conclusion, the Office stated that absent evidence of correlation of the marker to a disease state, one of ordinary skill in the art would not be able to predictably use the polynucleotides in any diagnostic setting without undue experimentation.

The fact that one of ordinary skill in the art would perhaps need to perform, for FDA approval purposes, additional validation studies of a prospective biomarker, and the fact that such studies might be considerable, are largely irrelevant and also not sufficient to support the Office’s contention that the claims are not enabled. Applicants respectfully point out that questions regarding diagnostic marker efficacy and validation, for example, are more properly left for agencies other than the Patent and Trademark Office. As set forth in the “Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph - Enablement Of Chemical/Biotechnical Application,” considerations made by the FDA for approving clinical trials and drug products are different from those made by the PTO in determining whether a claim is enabled. Clearly, validating biomarkers with respect to human clinical diagnostic efficacy is a task more properly within the purview of the FDA rather than the PTO.<sup>1</sup>

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<sup>1</sup> See also *In re Brana*: “The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed

If the Examiner is looking for evidence of drug safety or human testing as required for FDA approval, it is clear that this is more than the statute requires. The courts have long held that this is not a proper level of inquiry when determining utility and enablement under Title 35. For example, in *In re Watson*, 517 F.2d 465, 476 (C.C.P.A. 1975), the court stated “Congress has given the responsibility to the FDA, not to the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use ....” The U.S. Court of Appeals for the Federal Circuit has followed this lead, and made clear in *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994), that “[t]esting for the full safety and effectiveness of a [claimed invention] is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. It is clear that one can enable a claim of treating cancer without having FDA approval or having performed clinical trials.

### **Rejections Under 35 U.S.C. §102**

Claims 20, 21 and 24-31 stand rejected as allegedly anticipated by Eid et al. (Cancer Research 58, 2461-2468) as evidenced by Monia et al. (U.S. Patent 6,008,048). Applicants do not agree as the cited reference fails to teach the claimed methods.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. See *Verdegall Bros. v. Union Oil Co. of California*, 814 F2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Eid fails to anticipate every element of the claimed methods. The pending claims recite methods correlating decreased levels of sequences comprising SEQ ID NO:167 in patient samples as compared to non-cancerous samples to the presence of prostate or colon cancer. At no point

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compounds for treating cancer in humans. The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) (“Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.”).

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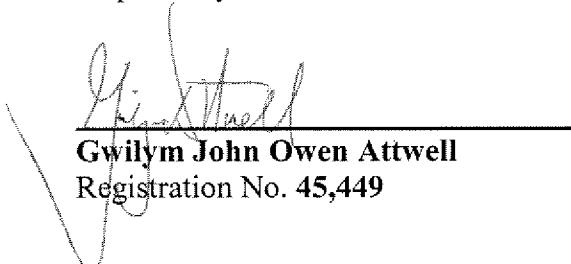
does Eid teach or even suggest such methods, as Eid does not disclose that *decreased* levels of sequences comprising SEQ ID NO:167 (i.e. Egr-1) in patient samples compared to control samples are indicative of prostate cancer. Indeed, as pointed out by the Office, Eid discloses that *increased* levels of Egr-1 in patient samples as compared to non-cancerous samples are indicative of prostate cancer. Accordingly, Eid cannot anticipate the claims. Applicants request withdrawal of the rejections under 35 U.S.C. § 102(b).

### Conclusion

The foregoing represents a bona fide attempt to advance the present application to allowance. Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney at (302) 778-8458 if such would expedite prosecution.

Applicant does not believe a fee is due for the filing of this response. If Applicant is incorrect, please charge Deposit Account No. 06-1050 for the required fee and apply any other charges or credits to Deposit Account 06-1050, referencing Attorney Docket No. 20366-005001.

Respectfully submitted,



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